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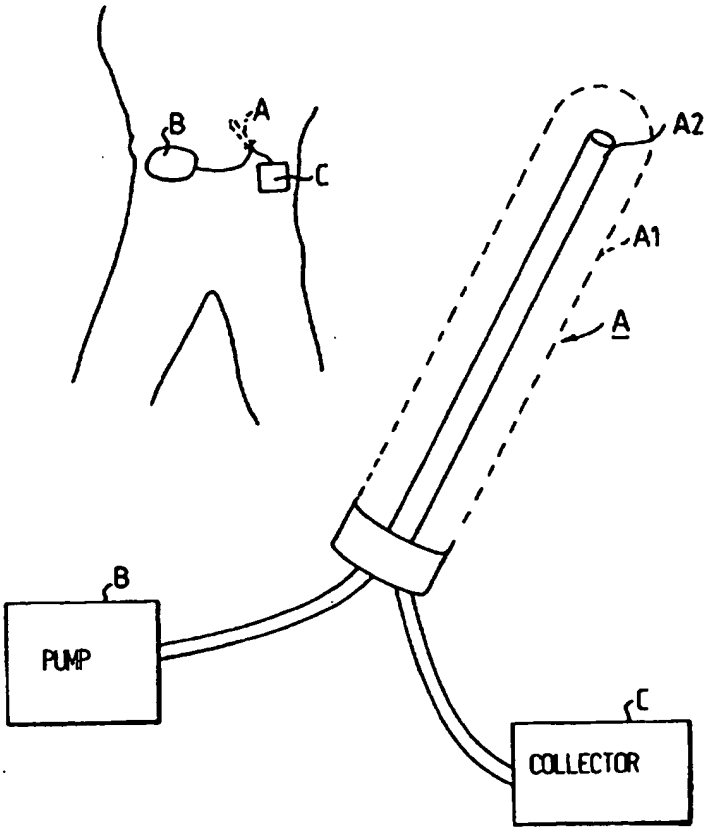
(54) Title: A MICRODIALYSIS DEVICE

(57) Abstract

Intermittent feed of dialysis fluid through a microdialysis catheter (A) is effected by a portable, battery-operated pump (B) in a controlled amount which corresponds to the active volume of the catheter (A) with no surplus and which is in the order generally of some tenths of a microliter. This provides the best sample concentration and a long battery life span, and a pump having small dimensions and capable of being carried firmly on the body of a patient.



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A MICRODIALYSIS DEVICE

The present invention relates to a microdialysis device of the kind which includes an elongated microdialysis catheter having a semi-permeable membrane included in a container, which together form an outer tube surrounding an inner tube, which has an opening at the distal end of the catheter, and a first line is connected to the proximal end of the inner tube and a second line is connected to the proximal end of a space formed between the inner tube and the outer tube, a pump for delivering dialysis liquid connected to one of the lines, and means for collecting through-pumped dialysis liquid from the free end of the second line. The invention also relates to a pump suitable for use with the device, and to a method suited for its operation.

A microdialysis catheter of this kind can be used for the in vivo performance of analyses of the different molecules contained in intercellular body fluids and capable of diffusing through the semi-permeable membrane. Microdialysis catheters can also be used to deliver different molecules via the dialysis liquid supplied.

A microdialysis catheter of the aforedescribed kind is known from SE-C-434 214. Small pumps for driving dialysis liquid through a catheter of this kind are also known to the art. These pumps normally include a cylinder and plunger of the kind used with injection syringes, and a drive means and motor for moving the plunger forwards in the cylinder. Such pump arrangements normally work continuously, although insulin pumps in particular may work intermittently, wherein insulin is delivered periodically and the supply of insulin is controlled by varying the amount delivered each time.

A particular feature with regard to microdialysis resides in the extremely small quantities of liquid required to fill a microdialysis catheter, namely quantities in the order of

less than 1 microliter, for instance 0.5 microliter, when compared with the fact that a droplet pouring freely from a narrow pipe is of the order of 15 microlitres.

In the case of stationary systems, it is normal and practical to work with continuous dialysis liquid throughflow. In the case of transportable systems, and particularly systems carried by a patient, which must be battery-operated, the requirement of low current consumption makes the use of intermittently operating pumps preferable. However, it has been found that commercially available apparatus are liable to provide excessively large quantities of sample fluid, in which the substances to be analyzed are lowly concentrated. Commercially available insulin pumps have also been found less suitable, because they are difficult and troublesome to handle. An object of the invention is therefore to provide an improved system, particularly with regard to the actual pump arrangement.

This and other objects are achieved in accordance with the invention by virtue of the pump of a system of the kind defined in the introduction is adapted to deliver intermittently on each intermittent pumping occasion a predetermined fluid quantity which is at most equal to roughly the volume that can be taken-up in the space between the inner tube and the outer tube over a length thereof that corresponds to th extension of the semi-permeable membrane in the longitudinal direction of the microdialysis catheter. This fluid volume will be in the order of 0.5 microliter in the case of a typical microdialysis catheter.

This results in improved efficiency, since only fluid that has been located close to th s mi-permeable membrane will be transported and replaced on each intermittent occasion. If a large quantity of fluid is replaced on each occasion, part of the outflowing fluid will never have been located in the zone in which exchange through the semi-permeable

membrane occurs, meaning that the fluid volume of interest from an analysis aspect will be unnecessarily diluted with fluid that lacks the factor to be analyzed. Using a signal analysis analogy, this means that the signal to noise ratio will be impaired.

The pump will also preferably have the possibility of executing an initial flushing process, in which all fluid in tube and catheter will be replaced, normally to an amount of roughly 100 µl. Optionally, this may be effected manually, prior to fitting a pump chamber and plunger constructed as an injection syringe into a motorized drive means, together forming a pump operative in pumping dialysis fluid through the microdialysis device. According to a particularly advantageous embodiment, the drive means has the form of a casing which accommodates the pump chamber and plunger and which is coupled to a battery-operated electric motor by means of a threaded screw, wherein the plunger has an extension externally of the pump chamber which has a perpendicularly disposed open bifurcate form which can be resiliently clamped about the screw, wherein at least one of the inwardly facing sides of the bifurcate form has a pattern of furrows or grooves whose periodicity coincides essentially with the pitch of the thread of the screw and a slope in relation to the direction of plunger movement which corresponds to the slopes of the threads on one side thereof against which the inwardly facing grooved side of the bifurcate form is resiliently disposed. In order to avoid the need to centre accurately, a particular advantage is afforded when only one side is provided with a screw-thread. The bifurcate form is preferably made of plastic, such as Delrin. The screw is preferably made of metal, conveniently of steel.

The invention will now be described with reference to a non-limiting embodiment thereof and also with reference to the accompanying drawings.

Fig. 1 illustrates schematically a microdialysis device with catheter, pump and sample-coll cting means.

Fig. 2 illustrates a microdialysis device fitted to a patient.

Fig. 3 is a block diagram illustrating a microdialysis pump.

Fig. 4 is a sectional view of a casing with drive means, for housing a pump chamber of the injection syringe kind and corresponding to a design illustrated in Fig. 3.

Fig. 5 illustrates a running nut which is intended to be fitted to the plunger rod of an injection syringe.

Fig. 6 is a cross-sectional view taken on the line IV-IV in Fig. 3.

Fig. 1 is a highly schematic illustration of a microdialysis device having a catheter A which is supplied with fluid by a pump B and which delivers fluid to a collector C. A semi-permeable membrane A1 forms an outer casing which surrounds a tube A2, and the tube A2 and the space defined between the tube A2 and the membrane A1 are each connected to a respective supply and drain tube connected to pump B and collector C respectively. The catheter A is normally inserted into tissue, as shown in Fig. 2, and a pump B according to the invention is attached to the patient's body, as is also a schematically indicated collector C.

The principle illustration in Fig. 3 shows the active components of a microdialysis pump, and a drive motor 1 which drives a screw 3 through the medium of a transmission 2. The screw is straddled by an open nut 4, as described in mor detail below, which is fastened to (or made integral with) the plunger rod of a pump corresponding to a syringe or the like 6. The power source has the form of a battery which is

controlled by a microcontroller 8 to deliver electric current to the motor 1, via a motor drive unit 9. The motor has a through-extending shaft and carries on the end thereof distal from the transmission gearing a code wheel 10 provided with dark and light stripes (not shown) which are sensed by an opto-sensor 11 (light source and light sensor in combination), which signals rotation of the motor to the microcontroller 8 via an opto-logic means.

As will be seen from the cut-away view shown in Fig. 4, the motor 1, the code wheel 10, the gearing and the screw 3 and the battery (7) are all neatly mounted in a housing 20. Remaining components are mounted on the circuit card 21 indicated in Fig. 4. Although not shown, an upper part is pivotally mounted at 22, wherein an injection syringe of the type intended for one-time use only and provided with a "straddle nut" 4 can be fitted and clamped firmly beneath the lid with the outlet end 13 of the syringe lying in an opening 23 and the plunger rod connected for translatory movement upon rotation of the screw 3.

This simple arrangement is made possible by using a nut 4, shown in more detail in Figs. 5 and 6, which includes a U-shaped recess whose one U-leg has a screw-thread 30 cut thereon, wherein the distance between the legs is adapted to the screw-thread on the screw 3.

In the case of one example, the screw measures M5 x 0.5 in accordance with SMS 1701, and the distance between the U-legs prior to cutting the thread is 4.5 mm. The straight cut threads 30 on the U-leg suitably define an angle of 1.95° to the cross direction of the nut. The nut may suitably be made of a plastic material, such as Delrin.

In the illustrated embodiment, the motor 1 is built together with a conventional gearbox 9 (not shown), so as to obtain a total ratio of 108:1 with the gearing 2. When using a

conventional disposable syringe (3 ml), the syringe will dispense 0.5 µl of fluid with each rotation of the motor. The screw has a pitch of 0.5 mm, and 1/108th rotation of the motor will result in a translation of about 4 µm. Since the motor always rotates in one and the same direction, any play that is present will have only a negligible effect.

When using a motor designed for a nominal 12 V, it is possible to obtain a suitable feed speed with a 4 V battery, wherein one revolution of the motor will take about one-tenth of a second. When the device is used intermittently and one motor revolution is performed each minute, battery consumption will be so low as to enable a battery to last for fifteen calendar days. However, the investigation period is seldom longer than three calendar days.

As before mentioned, when inserting a microdialysis catheter, it is necessary to undertake a filling and flushing period, which, e.g., may involve the discharge of 100 µl of fluid at a rate of 15 µl per minute and thus with one motor revolution each other second. Furthermore, all transmission plays and clearances will be levelled out during this time period. In the following sampling period, fluid is discharged at one revolution per minute, thus at a quantity of 0.5 µl intermittently.

This example relates to a microanalysis catheter having an effective volume of 0.5 µl or negligibly thereabove. When other microdialysis catheters are used, the pump must be adapted accordingly, since the concept is to replace the fluid in the active part of the catheter on each feed occasion, with no surplus fluid being pressed through and therewith diluting the sample solution. Although having no part of the present invention, it can be mentioned that individual sample volumes are normally collected during succ ssive time periods, for instance time periods of 15 min., 30 min. or 1 hr., depending on the speed at which, for

instance, metabolic developments change, such as the changes in the sugar values of diabetics or other changes. In other cases, the equipment is used to deliver substances to a patient, and this example should not therefore be considered all-inclusive.

It is pointed out that the arrangement shown in the cut-away view of Fig. 4 is roughly to scale, and it will therefore be readily seen that the arrangement can be carried by a patient, for instance as shown in Fig. 2, and that the patient will experience no appreciable discomfort and that the arrangement can be used in any situation whatsoever and even when taking working samples. The person skilled in this art will understand that the device can be attached to the body of the patient with the aid of a strap or with the aid of adhesive tape.

CLAIMS

1. A microdialysis device for connection to an elongated microdialysis catheter (A) having a semi-permeable membrane included in a holder which, together with the membrane, forms an outer tube in which an inner tube is housed, which has an opening at the distal end of the catheter, wherein a first line is connected to the proximal end of the inner tube and a second line is connected to a space formed between the inner tube and the outer tube at the proximal part of said space, a pump (A) which is connected to one of said lines and which delivers dialysis fluid, and means (B) for collecting from the end of the other one of said last-mentioned lines dialysis fluid that has flowed through the microdialysis device, **characterized** in that the pump is constructed to deliver a predetermined amount of fluid intermittently on each intermittent occasion, this amount being at most approximately equal to the volume that can be taken up in the space located between the inner tube (A2) and the outer tube (A1) above that part of the space which corresponds to the extension of the semi-permeable membrane in the longitudinal direction of the microdialysis catheter.

2. A device according to Claim 1, **characterized** in that the pump includes a casing (20) which houses a battery (7), an electric motor (1), gearing, a screw (3) which is connected to the screw via said gearing, and a replaceable injection syringe (6) comprising a cylinder and a plunger which moves in said cylinder and has a plunger rod which protrudes therefrom, a screw-threaded open nut means which can be brought into engagement with the screw at the distal end of said plunger, and a motor control means for advancing the plunger, preferably intermittently.

3. A device according to Claim 2, **characterized** in that a transmission means is provided between the motor (1) and the screw (3); and in that the motor control means includes a

sensor (10, 11, 12) which senses rotation of the motor.

4. A device according to Claim 2 or Claim 3, characterized in that the transmission means is such that one motor revolution corresponds to a pump feed in the order of some tenths of a microliter.

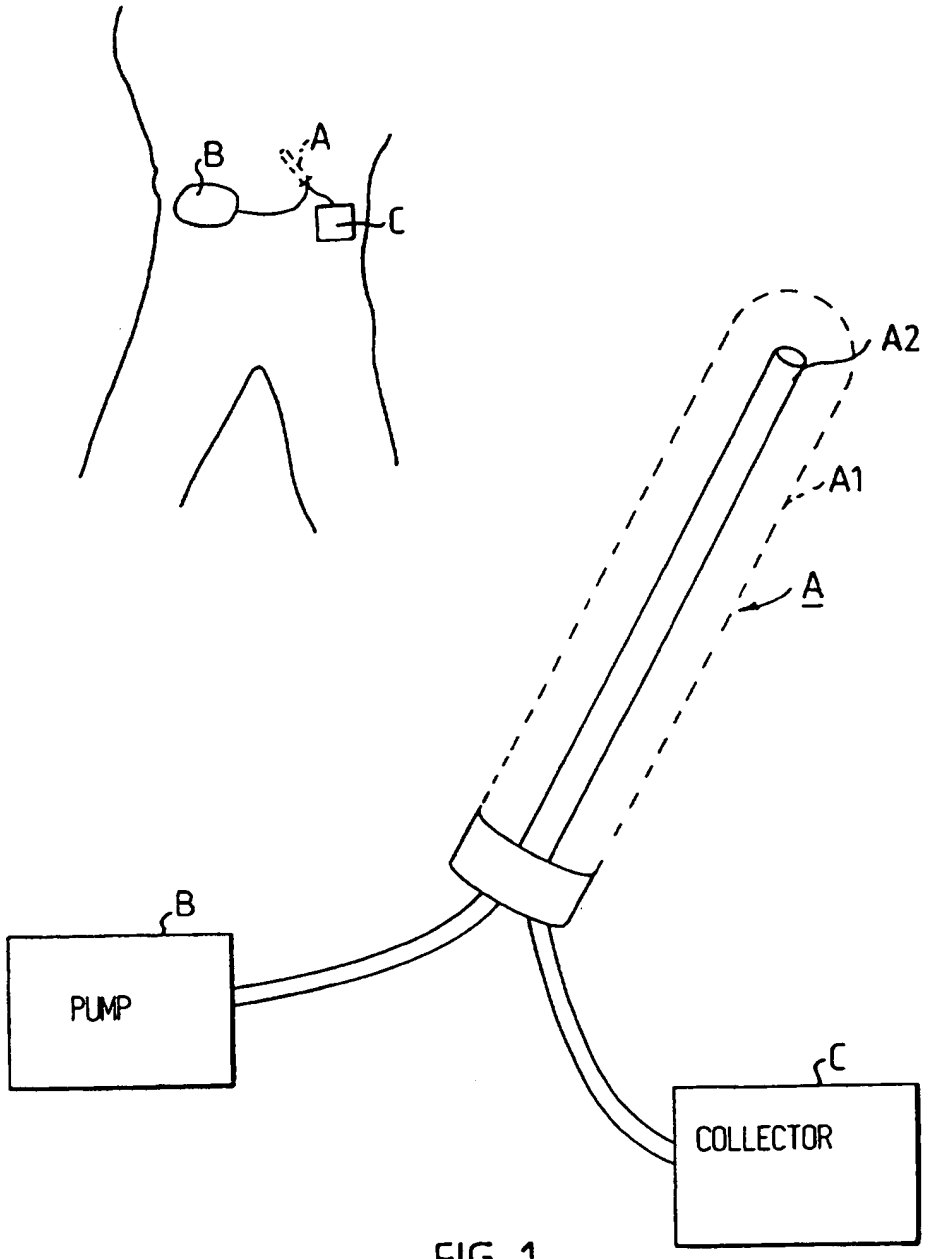

FIG. 1

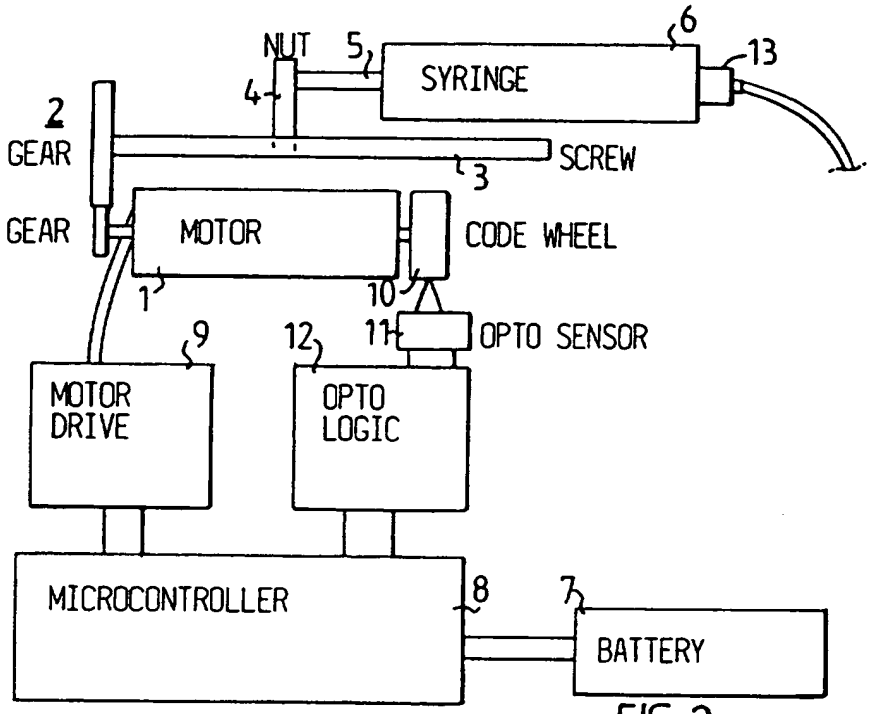

FIG. 2

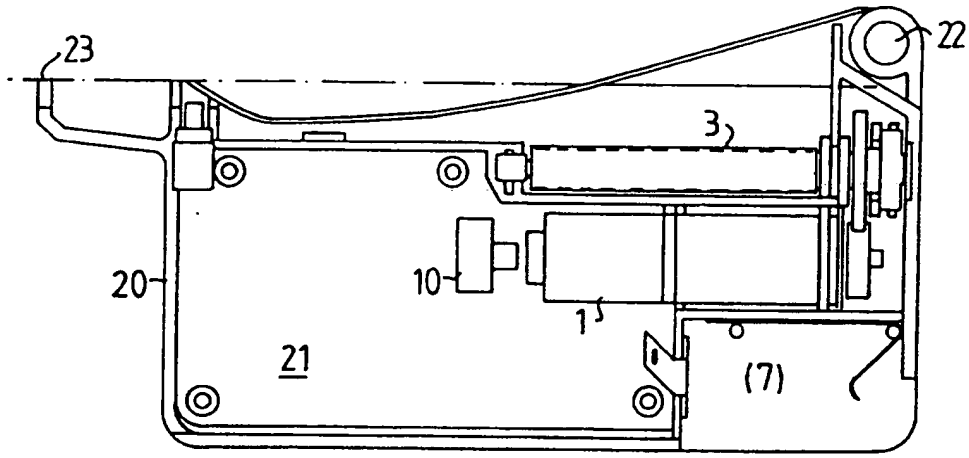

FIG. 3

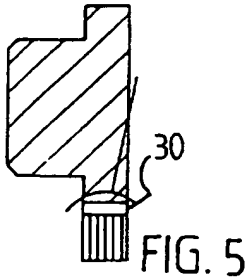

FIG. 5

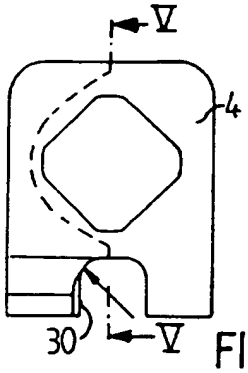

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01343

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61M 1/14, A61M 1/16, A61M 5/145
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9014791 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM), 13 December 1990 (13.12.90), page 3, line 31 - page 4, line 28, figures 1,2, abstract --	1
A	WO 8902720 A1 (STICHTING SCIENCE PARK GRONINGEN), 6 April 1989 (06.04.89), page 17, line 11 - line 20, figures 1,3, claim 4, abstract --	1
A	WO 9218191 A2 (THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS), 29 October 1992 (29.10.92), figures 1-6, abstract --	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	AU 607982 B (BIONICA PTY LIMITED), 21 March 1991 (21.03.91), page 11, line 22 - line 30, figures 1, 8,10, abstract -- --------	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/02/96

International application No.
PCT/SE 95/01343

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		US-A- 5078135	07/01/92
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		JP-T- 3505516	05/12/91
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		EP-A,A,A 0285403	05/10/88
		US-A- 4919650	24/04/90